Physicochemical stability of Cefotaxime sodium in Polypropylene Syringes at High Concentrations for Intensive Care Units

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Introduction

In ICUs, the dose of cefotaxime can vary from 3 g to 24 g per day and continuous administration is the preferred mode of administration.

Patients with fluid restriction → **Minimum volume and high dose** → **High concentrations of cefotaxime**

Objectives

Physicochemical stability studies of cefotaxime sodium solutions

- **Concentrations :** 83.3 and 125 mg/mL
- **Container**: polypropylene syringes
- **Solvent**: sodium chloride 0.9% (NaCl 0.9%) - glucose 5% (G5%)
- **Storage** : 20-25°C, unprotected from light
- **Analysis** after preparation, and after 6 and 12 hours.

Materials and Method

Chemical stability

① **RP-HPLC with DAD detector at 235 nm**

- **Column**: C18 LiChrospher® 12.5 cm, particle size=5 µm at 30°C
- **Mobile phase**: gradient mode

Phase A : 86 % Na_2HPO_4 buffer 0.05 M, pH=6.25 and 14 % of methanol
Phase B : 60 % Na_2HPO_4 buffer 0.05 M, pH=6.25 and 40 % of methanol

- **Flow rate** at 1.3 mL/min
- **Injector temperature** at 15°C
- **Injection volume**: 10 µL

Physical stability

➢ **Visual examination** : change of colour, precipitation, gaz formation

② **Validation of the method as recommanded by ICH Q2(R1)**

- **Forced degradation**

Acidic	Alkaline	Oxydative	Heat
HCl 0.05 M 3h	NaOH 0.01 M 5 min	H_2O_2 0.30 %	40°C 7h

- **Linearity :** standard curve with 5 points : 50-150 µg/mL
- **Repeatability and intermediate precision**

③ **pH measurement** (Bioblock Scientific pH meter)

➢ **Subvisual examination** : turbidimetry by spectrophotometry at 350, 410 and 550 nm (Safas Monaco UV m²)

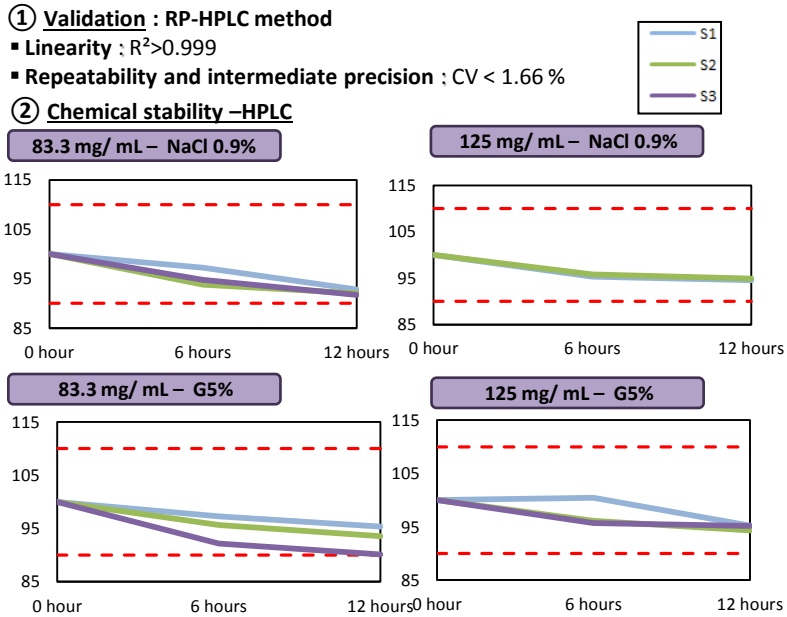
→ **3 syringes for each condition (S1 – S2 – S3)**

Results

① **Validation : RP-HPLC method**

- **Linearity** : R^2>0.999
- **Repeatability and intermediate precision** : CV < 1.66 %

② **Chemical stability –HPLC**

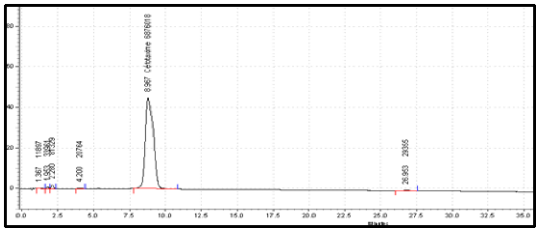


pH measurement
→decreased slighly
Maximum variation :
T0 → T12h : 0.5 pH unit
[5,32 → 4,82]

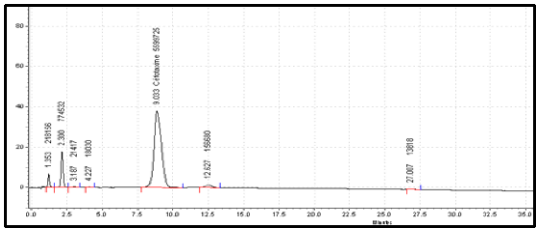
③ **Physical stability**

- *Visual aspect* : ↗ of the intensity of the yellow colour
- *Sub-visual aspect* : ↗ of the absorbance values progressively of each wavelength and each condition.

- **Stability indicating capacity**



Chromatogram of cefotaxime sodium 100 µg/mL in NaCl 0.9% without stressed conditions.



Chromatogram of cefotaxime sodium 100 µg/mL after alkaline stressed conditions (NaOH 0.01 M, 5 min)

Additional peak (Relative retention = 3.01)
↗ Up to 4.01% in NaCl 0.9%
↗ Up to 3.17% in G5%
} at T=12 hours
of the total surface area of the peaks.

Conclusion

Chemical stability of cefotaxime solutions for each condition → **Physical modification of cefotaxime** after a 12-hour storage → **Limitation of the stability** for cefotaxime at 83.3 and 125 mg/mL at **6 hours** for G5% and NaCl 0.9%.